Neurocognitive Processes Associated with Reduced Inhibitory Control of Prepotent Eye Movements in Autism Spectrum Disorder

By

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Abstract

Impairments in inhibitory control (IC), or the ability to suppress a dominant behavioral response, are common in individuals with autism spectrum disorder (ASD). Multiple psychological and neurophysiological processes contribute to successful IC, though the extent to which these distinct processes are affected in ASD is not known. We previously have documented that individuals with ASD show a reduced ability to proactively delay response onset during a manual stop-signal task which contributes to failures inhibiting contextually inappropriate responses. Relative to manual movements, eye movements are highly automated, more difficult to inhibit, and more closely linked to discrete neurophysiological processes. Characterizing IC of eye movements in ASD may provide key insights into spared and affected psychological and neurophysiological processes. Sixty individuals with ASD aged 5-29 years and 63 age- and gender-matched typically developing controls completed an oculomotor stop-signal task (i.e., countermanding). During this task, the majority of trials were GO trials, on which participants made rapid eye movements (i.e., saccades) toward peripheral targets (12 degrees to the left or right of center). The remaining trials were STOP trials, on which a stop signal appeared at variable intervals following the peripheral target (i.e., stop signal delays) to cue the participant to inhibit the saccade. Stopping accuracy (i.e., the percent of STOP trials successfully inhibited), estimated reaction time of the stopping process (SSRT), and reaction time slowing on GO trials (GO RT slowing) compared to a baseline reaction time task were examined. Individuals with ASD exhibited reduced stopping accuracy and GO RT slowing and faster SSRTs compared to controls. For both groups, stopping accuracy was positively related to GO RT slowing and not related to SSRT. Increased age was associated with higher stopping accuracy and GO RT slowing, and these relationships did not differ across groups. The results indicate that individuals with ASD show a reduced ability to inhibit and proactively delay prepotent eye movements,

while reactive stopping abilities are unaffected. Impaired IC was strongly and selectively associated with deficits in their ability to strategically delay response onset rather than reactively inhibit responses. These findings implicate reduced top-down control via fronto-striatal inhibition of brainstem circuitry in ASD, provide new targets for addressing clinical issues of IC, and suggest that tests of proactive control of eye movements may be useful for testing treatment efficacy and clarifying neurophysiological mechanisms of key clinical outcomes in ASD.

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Introduction

Autism spectrum disorder (ASD) is defined by impairments in social communication and the presence of restricted and repetitive behaviors (RRBs; American Psychiatric Association, 2013). Determining the neurocognitive processes associated with these key symptoms is important for establishing a more mechanistic understanding of the disorder and informing the development of more targeted interventions. Numerous studies have suggested that broader executive functions are compromised in individuals with ASD (e.g., Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004). However, the discrete processes that are affected have been more difficult to define due to inherent challenges in parsing elemental operations during complex neuropsychological tests and reliance on relatively small sample sizes in which participants may vary widely in terms of the nature and severity of their clinical symptoms.

Inhibitory control is a more circumscribed neurocognitive operation that has been consistently implicated in ASD (Agam, Joseph, Barton, & Manoach, 2010; Mosconi et al., 2009; Thakkar et al., 2008). Inhibitory control is defined as the ability to suppress a dominant behavioral response, and it is necessary for the appropriate adjustment of behavior in response to changing environmental demands (Logan, 1985). Individuals with ASD show reduced inhibitory control of multiple behavioral response types (Adams & Jarrold, 2012; Mosconi et al., 2009; Schmitt, White, Cook, Sweeney, & Mosconi, 2018), and these deficits appear to be familial (Mosconi et al., 2010) and associated with the severity of clinical issues (Mosconi et al., 2009; Schmitt et al., 2018). Schmitt et al. (2018) recently demonstrated that *proactive control* strategies involved in slowing entrained hand movements (e.g., button presses) during conditions of uncertainty underpinned inhibitory control deficits in ASD, whereas *reactive control* processes, such as the ability to rapidly terminate a behavioral response, were relatively intact in patients.

These findings are important in the context of neurophysiological data indicating that distinct patterns of activation in fronto-striatal brain circuits support proactive and reactive control processes during behavioral response inhibition (Aron, 2011; Aron, Robbins, & Poldrack, 2014). Based on evidence that strategically slowing responses is more difficult for eye movements than for hand movements due to their greater automaticity (Schmitt, Ankeny, Sweeney, & Mosconi, 2016), tests of proactive and reactive control systems during inhibition of eye movements in ASD offer a sensitive method for determining the extent to which these distinct neurocognitive processes are affected in patients.

The stop signal task (SST) is a frequently studied test of inhibitory control that provides separate measures of proactive and reactive control processes (Logan & Cowan, 1984). During this task, the majority of trials are "GO" trials on which participants are instructed to respond to a target stimulus (GO cue; e.g., a visual stimulus) with a motor response (e.g., making an eye movement toward the stimulus) as quickly as possible. A minority of trials are "STOP" trials during which the GO cue is followed by a stop signal alerting the participant to inhibit the response. Multiple studies of the SST have supported an "independent race model" which posits that two independent processes in the brain, the GO and STOP processes, race against each other to determine whether the participant responds (see Figure 1; Logan & Cowan, 1984). If the GO process finishes first, the participant responds; if the STOP process finishes first, the participant successfully inhibits, and the result is no response.

Proactive control during this task involves preparatory delaying of the GO process which is reflected by longer reaction times on GO trials (GO RTs). Proactive control serves to increase the likelihood that the STOP process will finish before the GO process if a stop signal is presented (Aron, 2011; Verbruggen & Logan, 2009). GO RT slowing can be measured by

subtracting reaction times (RTs) on a baseline task from GO RTs during the SST. The baseline RT task differs from the SST in that it is composed solely of GO trials so that there is no risk of a stop signal appearing. Typically developing (TD) individuals show slower RTs on GO trials during the SST relative to baseline RTs due to the uncertainty about whether a stop signal will appear (Schmitt et al., 2016; Verbruggen & Logan, 2009; Vink et al., 2014). Our group and others have found that the extent to which individuals slow their GO RTs is highly associated with an increased percentage of successful STOP trials (Lo, Boucher, Pare, Schall, & Wang, 2009; Schmitt et al., 2016; Verbruggen & Logan, 2009).

Reactive inhibitory control can be estimated during the SST by the stop signal reaction time (SSRT; Aron, 2011). The SSRT is an estimate of the RT of the individual's STOP process. SSRT cannot be measured directly, but several approaches have been developed to calculate it based on each individual's GO RTs, the percent of STOP trials successfully inhibited, and the average time between the GO cue and the stop signal (i.e., the stop signal delay, or SSD). For example, the distribution of each individual's GO RTs can be used to determine the timepoint above which the proportion of GO RTs is equal to the proportion of STOP trials successfully inhibited. This timepoint represents the average time at which the STOP process is completed. The average SSD, which represents the average time that the STOP process started, is then subtracted from this timepoint and the result is the individual's SSRT (Logan & Cowan, 1984). This procedure has been validated across numerous studies and is associated with individuals' stopping ability (Boucher, Stuphorn, Logan, Schall, & Palmeri, 2007; Hanes & Schall, 1995).

The current study used an oculomotor SST to examine reactive and proactive inhibitory control processes in ASD. We predicted that individuals with ASD would show reduced stopping accuracy (i.e., percent of STOP trials successfully inhibited) and reduced GO RT slowing

compared to controls. It also was hypothesized that these deficits would be strongly related to one another suggesting that inhibitory control deficits in ASD are related to a reduced ability to strategically slow responses. Consistent with our prior manual SST findings, we hypothesized that there would be no difference in SSRT between groups indicating that reactive inhibitory control is relatively unaffected in ASD. We also examined whether inhibitory control abilities varied in relation to age and clinical severity in ASD.

Method

Participants

Sixty individuals with ASD and 63 TD controls matched on age (range: 5-29 years; mean: 14+/-6) and gender completed an oculomotor SST task either at the University of Illinois at Chicago (UIC; n=80) or the University of Texas Southwestern Medical Center (UTSW; n=43; Table 1). Ratios of participants with ASD to TD controls were similar across the two sites (1.05: 1 at UIC and 0.79: 1 at UTSW). Participants with ASD were recruited through outpatient clinics and advertisements in the community. The diagnosis of ASD was confirmed using the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003), the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2012), and expert clinical opinion based on DSM-5 criteria. TD control participants were recruited from community advertisements and word of mouth, and were excluded if they scored ≥ 8 on the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003), had a history of psychiatric illness, had a first-degree relative with a major psychiatric illness, had a first-degree or second-degree relative with ASD, or were taking a medication known to affect cognitive or oculomotor abilities including antipsychotics and anticonvulsants (Reilly, Lencer, Bishop, Keedy, & Sweeney, 2008). Two participants with ASD were taking antidepressants at the time of

testing. All potential participants were excluded if they had a known metabolic or genetic disorder associated with ASD such as Fragile X Syndrome, or if they had suffered a severe head injury or one that resulted in a loss of consciousness. Participants were required to refrain from consuming caffeine within 24 hours before testing and nicotine within one hour before testing. Adult participants provided written consent, and minors provided written assent in addition to their legal guardians' written consent. The study procedures were approved by the local Institutional Review Board.

Procedure

Participants sat in a darkened black room 60 cm from a 102 cm anti-glare LCD monitor (resolution: 1920 x 1060). Due to technical issues at UIC, the first 20 participants (12 with ASD, 8 TD controls) completed testing on a monitor with a refresh rate of 75 Hz, and the subsequent 60 participants completed testing on a monitor with a refresh rate of 120 Hz (29 with ASD, 31 TD controls). UTSW participants completed testing on a monitor with a refresh rate of 60 Hz (19 with ASD, 24 TD controls). At both sites, a chin rest with occipital restraints was utilized to limit participants' head mobility. At UIC, participants' eye movements were obtained using infrared (IR) sclera-reflection sensors mounted on spectacle frames (Model 310, Applied Science Laboratories, Bedford, MA). Blinks were monitored using direct current electro-oculography (EOG; Grass Neurodata 12 Acquisition System; Astro-Med, Inc., West Warwick, RI). EOG electrodes were placed above and below the left eye and were linked to an AC-coupled bioamplifier. Eye movement signals were collected at 500 Hz with a 12-bit A/D converter (DI-720 from Dataq Instruments, Akron, OH). At UTSW, eye movements were obtained using an infrared, binocular camera-based eye tracking system with a 500 Hz sampling rate (EyeLink II, SR Research Ltd., Canada). Participants performed a nine-point calibration before each block of

trials. Digital finite impulse response filters with non-linear transition bands were applied. Data from each trial were visually inspected and scored without knowledge of subject characteristics.

SST. During the oculomotor SST, participants completed GO and STOP trials (Figure 2). At the start of each trial, subjects fixated on a white crosshair in the center of the screen. Participants were required to fixate on the central crosshair (i.e., within $\pm$ 3 degrees) for at least 500 ms before the trial would initiate. After a variable amount of time (1500-2000 ms, or longer if the participant did not maintain fixation), the central crosshair disappeared and the GO cue (a white circle) appeared 12 degrees to the left or right of center. For GO trials, subjects were instructed to look at the GO cue as quickly as possible. If subjects did not respond within 650 ms of the appearance of the GO cue, the target disappeared and a red "X" took its place with the word "faster" below it. This negative feedback was provided to discourage subjects from waiting indefinitely for the appearance of a stop signal. For every three trials on which the participant reached this 650 ms limit, an additional GO trial was presented later in the task. A response on a GO trial was considered correct if the saccade velocity exceeded 30 degrees per second, saccade amplitude exceeded four degrees in the correct direction, and the saccade reached at least half the distance between the central fixation and the target (6 degrees).

On STOP trials, a red stop sign (i.e., the stop signal) appeared at the center of the screen after the appearance of the GO cue. For testing conducted at UIC, the stop signal delay (SSD), defined as the interval between the onsets of the GO cue and stop signal, varied randomly between 50 and 200 ms and was sampled continuously to match the refresh rate of the monitor. Therefore, SSD varied by 13.33 ms or 8.33 ms for the 75 Hz or 120 Hz monitors respectively. For participants tested at UTSW, SSD varied between 50 and 233 ms and was sampled every 16.67 ms. Subjects were instructed not to look at the GO cue if the stop signal appeared. If

participants made saccades during STOP trials, a red "X" would appear in the center of the screen. At UIC, the task included 150 (66%) GO trials and 75 (33%) STOP trials, which were divided into three blocks of 75 trials (225 total trials). At UTSW, the task included 72 (60%) GO trials and 48 (40%) STOP trials, which were divided into four blocks of 30 trials (120 total trials). GO and STOP trials were administered in a pseudorandom order, and no more than three trials of the same type were administered consecutively. A 10 second rest period was presented after each block. Accuracy on STOP trials, RT during GO trials, and SSRT were examined. To calculate SSRT, the previously developed "integration method" was used (Hanes & Schall, 1995; Logan & Cowan, 1984). Briefly, the proportion of total STOP trials the participant failed to inhibit is determined. Then, the distribution of RTs on GO trials for each participant is listed in ascending order. The RT at which the proportion of GO RTs equals the proportion of failed STOP trials is identified, and the average SSD, which represents the average time that the STOP process was initiated, is then subtracted from this RT. The result is the estimated time it takes the STOP process to complete, or the SSRT. SSRTs were calculated separately for each participant and direction of the GO cue (left vs. right).

Prior to completing the SST, participants completed a baseline RT task consisting of 30 GO trials. During the baseline task, participants fixated on a crosshair for a variable interval (1500-2000 ms) and shifted their eye gaze to peripheral targets appearing at 12 degrees to the left or right of center. Target location was varied pseudorandomly. RTs on this task were subtracted from GO trial RTs during the SST to determine the extent to which each participant slowed their RTs during uncertainty.

Clinical Measures. Participants completed one of three tests of general cognitive ability based on age and study site. Participants at the UIC location < 18 years completed the

Differential Ability Scale, Second Edition (31 with ASD, 29 TD controls; DAS; Elliott, 2007), and those ≥ 18 years old completed the Wechsler Abbreviated Scale of Intelligence (WASI; 10 with ASD, 12 TD controls; Wechsler, 2011). For UTSW, participants ≥ 6 years completed the WASI (18 with ASD, 22 TD controls), and those < 6 completed the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI; 0 with ASD, 2 TD controls; Wechsler, 2012), with the exception of one 13-year-old individual with ASD who completed the DAS.

To assess ASD severity, the ADOS-2 was administered and a parent or caregiver completed the ADI-R and the Repetitive Behavior Scale-Revised (RBS-R; Bodfish, Symons, Parker, & Lewis, 2000). The ADOS-2 is a semi-structured play and conversation-based assessment of social and communicative skills and repetitive behaviors. As different modules of the ADOS-2 include different items in their total score algorithms, alternate scores were calculated for participants who were administered Module 4 to align with Module 3 algorithms and scores were combined across modules as done previously (Schmitt et al., 2018). The ADI-R is a semi-structured interview administered to parents or caregivers of individuals suspected of having ASD. The ADI-R assesses social impairments, communication abnormalities, and restricted, repetitive behaviors. The ADOS-2 and ADI-R each were administered by research reliable clinicians. The RBS-R is a parent/caregiver questionnaire measuring repetitive behaviors characteristic of ASD. Higher scores on all three of these measures indicate more severe symptoms.

Statistical Analyses

To examine SST performance across groups, three multilevel model (MLM) analyses were conducted in which trial effects (e.g., SSD, direction of stimulus) were identified as level 1 predictors and subject effects (e.g., group, age) were identified as level 2 predictors. This

approach allows for the examination of within-subject and between-subject fixed effects while allowing within-subject effects to differ for each participant (random effects). To identify the most parsimonious and best-fitting models, variables that did not significantly improve model fit ($p > .05$) were removed from the final models (Hox, Moerbeek, & van de Schoot, 2017). Whether each variable improved model fit was determined through comparisons of nested models (i.e., models that are identical except that only one includes the variable of interest) using likelihood ratio tests. All predictors across the three MLM analyses were centered. Due to differences in testing conditions between sites and differences in IQ between groups, site and nonverbal IQ were included in analyses of stopping accuracy, GO RT, and SSRT.

The first MLM analysis examined stopping accuracy. As accuracy is binary at the trial level (correct vs. incorrect), a generalized multilevel model with a logit link function was used (Hox, Moerbeek, & van de Schoot, 2017). Initial models examined level 1 fixed effects of SSD (including linear, quadratic, and cubic effects) and direction (left vs. right), level 2 fixed effects of group (TD vs. ASD), age (including linear, quadratic, and cubic effects), and sex (male vs. female), all two- and three-way interactions, and random variance components for the intercept and level 1 variable slopes (SSD and direction). Only trials with SSDs within the range that overlapped between the two testing sites (between 50 and 200 ms) were examined.

Separate linear MLM analyses were used to examine GO trial RT and SSRT. To assess RT, preliminary models examined level 1 fixed effects of task (baseline vs. SST) and direction (left vs. right), level 2 fixed effects of group (TD vs. ASD), age (including linear, quadratic, and cubic effects), and sex (male vs. female), all two- and three-way interactions, and random variance components for the intercept and level 1 variable slopes (task and direction). For SSRT, preliminary models examined a level 1 fixed effect of direction (left vs. right), level 2 fixed

effects of group (TD vs. ASD), age (including linear, quadratic, and cubic effects), and sex (male vs. female), a group x direction interaction effect, and a random variance component for the intercept. One participant in the ASD group did not have any correct STOP trials (0% STOP accuracy) in one direction which prevented us from being able to calculate their SSRT for that direction; this participant was excluded from all analyses including SSRT. Relationships between stopping accuracy and GO RT slowing and between accuracy and SSRT were examined using Pearson correlations.

Spearman correlations also were conducted to examine the relationships between SST performance and clinical ratings of ASD based on the ADOS Social-Communication algorithm, the ADI-R Reciprocal Social Interaction, Communication, and RRB (separated into higher-level and lower-level behavior) Current Behavior algorithms, and the RBS-R Stereotyped, Self-injurious, Compulsive, Ritualistic, Sameness, and Restricted Behavior algorithms. ADOS RRB measures were not examined due to the relatively low test-retest reliability of the algorithm (e.g., Hus & Lord, 2014). The Holm's Bonferroni procedure was used to reduce risk of Type 1 error due to multiple comparisons (Abdi, 2010).

Results

Final model results for stopping accuracy, RT slowing, and SSRT are presented in Table 2. Individuals with ASD demonstrated reduced stopping accuracy compared to controls (Table 3; Figure 3A; β = -0.387, p = 0.012). The relationship between SSD and stopping accuracy was best described by a quadratic model in which accuracy decreased as SSD increased, and the rate at which accuracy decreased slowed at longer SSDs (Figure 3A; SSD: β = -0.810, $p < 0.001$; SSD^2: β = -0.089, p = 0.032). The group x SSD quadratic effect approached significance (group x SSD: $\chi^2(1) = 3.804$, p = 0.051) and reflected greater difference between groups on trials with shorter

SSDs compared to those with longer SSDs. For both groups, increased age was associated with higher stopping accuracy (β = 0.225, p = 0.004), though the effects of age on stopping accuracy did not vary as a function of group (group x age: $\chi^2(1)$ = 0.014, p = 0.903).

RTs on GO trials during the SST were slower than baseline RTs (task effect: β = 88.926, p < 0.001). RT slowing was reduced for individuals with ASD compared to controls (Figure 3B; group x task interaction: β = -22.973, p = 0.005). Increased age was positively associated with RT on SST GO trials but not baseline trials (task x age interaction: β = 25.747, p < 0.001). Individuals with ASD had shorter SSRTs compared to TD controls (Table 3; Figure 3C; β = -13.322, p = 0.035), and increased age was associated with longer SSRTs in both groups (β = 7.847, p = 0.014).

For both groups, higher stopping accuracy was associated with increased RT slowing (Figure 4A; r = 0.585, p < 0.001), and this effect was similar for individuals with ASD (r = 0.674, p < 0.001) and controls (r = 0.449, p < 0.001; Z = 1.81, p = 0.070). Stopping accuracy was not associated with SSRTs for either group (Figure 4B; total: r = -0.071, p = 0.437; ASD: r = -0.100, p = 0.452; TD: r = -0.138, p = 0.279). Full-scale IQ was not related to SST accuracy, RT slowing, or SSRT for either group. After correcting for multiple comparisons, no relationships between SST performance and clinical ratings of ASD symptoms were observed. Based on our findings that all three measures of SST performance showed age-related differences, partial correlations were conducted examining the relationships between SST performance and clinical symptoms of ASD controlling for age (Table 4). No relationships between SST performance and clinical symptoms were identified.

Discussion

In the current study, we demonstrate that individuals with ASD show a reduced ability to inhibit contextually inappropriate prepotent responses, and that this failure is strongly and selectively associated with deficits in their ability to strategically delay response onset during conditions of uncertainty. These results are consistent with our previous findings that individuals with ASD have reduced abilities to inhibit and delay button presses (Schmitt et al., 2018), and extend these findings to indicate that successful inhibition of highly automated eye movements is impaired in ASD and relies on proactive inhibitory control processes.

By demonstrating that failures to inhibit prepotent behaviors are strongly associated with deficits of proactive control, our results indicate that preparatory mechanisms required for the successful inhibition of eye movements are impaired in ASD. Looking toward a suddenly appearing stimulus is a reactive, ballistic response characterized by faster RTs than most limb movements (Adams, Milich, & Fillmore, 2010; Boucher, Stuphorn, et al., 2007; Schmitt et al., 2016). The automaticity of exogenously driven eye movements in an oculomotor SST (i.e., those elicited by the sudden appearance of a visual cue) increases the difficulty of suppressing reactive eye movements relative to limb movements (Boucher, Stuphorn, et al., 2007; Schmitt et al., 2016) or volitional eye movements (Logan & Irwin, 2000). Our findings that overall stopping ability is strongly related to proactive, but not reactive, control for both individuals with ASD and TD controls suggests that proactive control mechanisms are necessary for the inhibition of highly automated responses. Our study also demonstrates that proactive control processes show age-associated improvements in individuals with ASD and TD controls across adolescence and into early adulthood, suggesting that targeted treatments aimed at supporting inhibitory control development in ASD may be effective over a prolonged course of development.

In contrast to previous studies from our group and others indicating either no difference in SSRT between groups (Ozonoff & Strayer, 1997; Schmitt et al., 2018) or slower SSRTs in ASD relative to TD (Lemon, Gargaro, Enticott, & Rinehart, 2011), we found that individuals with ASD exhibit faster SSRTs than controls indicating faster reactive control during oculomotor response inhibition. However, despite these faster SSRTs, individuals with ASD do not reach typically developing levels of stopping accuracy, supporting the conclusion that performance on an oculomotor SST task relies primarily on the ability to proactively delay responses rather than to quickly react to the stop signal. Age-associated differences in SSRT were similar for both individuals with ASD and TD controls, indicating that inclusion of a broad age range does not explain the divergence between our findings and prior studies. Overall, our findings suggest that individuals with ASD respond faster than TD controls to visual stimuli during the SST. Since individuals with ASD have similar RTs to controls when making visually guided saccades in the current study (i.e., at baseline) and previously (Mosconi et al., 2009; Schmitt et al., 2014), our findings indicate an overall pattern of slowing in TD controls relative to ASD when it is advantageous to wait for relevant stimuli before responding.

The differences between groups on SST performance in the current study are moderate for stopping accuracy (d = 0.44) and GO RT slowing (d = 0.44). These effects are similar to that identified in a meta-analysis of prepotent inhibitory control in ASD (Geurts, van den Bergh, & Ruzzano, 2014; d = 0.55). However, as the demanding nature of the SST (e.g., long task duration and requirement to maintain consistent fixation prior to the onset of each trial) may have narrowed current sample to those cognitively and behaviorally able to complete such a task, these effect sizes may be larger in more inclusive sample. The larger between group difference in

stopping accuracy at shorter SSDs suggests that future tests focusing on this range of SSDs may demonstrate stronger between group effects.

One key advantage of our approach for studying inhibitory control is that it is highly translational. Specifically, the discrete physiological mechanisms supporting inhibitory control and proactive strategies during eye movements have been examined at the cellular level in non-human primates. Single-cell recording studies in rhesus monkeys have identified neurons in frontal eye fields and superior colliculus that selectively fire when preparing for or executing a saccade (movement neurons) or while fixating on a single location (fixation neurons; Hanes, Patterson, & Schall, 1998; Pare & Hanes, 2003). Firing rates of movement and fixation cells then modulate activity of omnipause and burst cells in the brainstem which determine whether an eye movement is made (Boucher, Palmeri, Logan, & Schall, 2007). The spiking neural circuit model posits that top-down inhibition of movement cells and concomitant firing of fixation cells of rostral superior colliculus lead to increased stopping accuracy and increased RTs on GO trials during the SST (Lo et al., 2009). This top-down inhibitory control is governed by fronto-striatal pathways including dorsolateral prefrontal cortex, frontal eye fields, caudate nucleus, and substantia nigra (Boucher, Palmeri, et al., 2007; Leung & Cai, 2007; Mosconi & Sweeney, 2015). Therefore, our findings implicate reduced top-down control via fronto-striatal inhibition of brainstem circuitry in ASD, contributing to a reduced ability to inhibit contextually inappropriate behaviors and delay behavioral response onset.

Although the current study provides new insight into behavioral inhibition impairments in ASD, several limitations also should be noted. Previously, we have identified positive relationships between inhibitory control and the severity of restricted and repetitive behaviors in ASD (Mosconi et al., 2009; Schmitt et al., 2018). Although some relationships were observed

between SST performance and social-communication symptoms, no relationships with clinical variables survived corrections for multiple comparisons. This may be due to inherent limitations of the subjective, clinically-rated measures used to assess the complex and diverse symptoms involved in ASD. Dimensional clinical rating scales across a range of behavioral and cognitive domains are needed to clarify clinical outcomes related to reduced inhibitory control in ASD. Second, as the sample of individuals with ASD was limited to those with IQ scores >70 and those who were not currently taking medications that could affect task performance, our results may not be fully generalizable to the broader ASD population. Third, longitudinal studies of inhibitory control abilities in ASD are needed to clarify the development of proactive and reactive inhibition throughout childhood and adolescence and identify optimal windows for intervention. Finally, while previous literature on the neurophysiological processes of oculomotor inhibition provide viable hypotheses regarding affected brain circuits, neuroimaging and electrophysiological studies are important for determining patterns of fronto-striatal dysfunction associated with reduced inhibitory control in ASD.

Our oculomotor SST provides a sensitive, biologically-linked, and objective measure of key neurocognitive impairments in ASD that may be useful for tracking clinical and treatment outcomes in patients. Our results indicate individuals with ASD show impairments of proactive inhibitory control processes that disrupt their ability to terminate or suppress contextually inappropriate behaviors. This pattern of behavioral impairments suggests a specific alteration in top-down control of action processes in anticipation of the possible need to inhibit that may be an important target for studies aimed at clarifying neurophysiological mechanisms of ASD.

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Table 1

Demographics of ASD and TD participants by site

	ASD			TD		
	UIC (n=41)	**UTSW (n = 19)**	**Total (n=60)**	**UIC (n=39)**	**UTSW (n = 24)**	**Total (n=63)**
Age	14.5 (5.3)	13.0 (3.5)	14.0 (4.9)	15.7 (7.0)	13.3 (5.3)	14.7 (6.5)
Male n (%)	32 (78)	17 (89)	49 (82)	29 (74)	19 (80)	48 (76)
NVIQ	101.2 (15.6)	101.8 (18.9)	101.4 (16.6)*	107.5 (11.9)	105.8 (11.1)	106.8 (11.6)*
VIQ	97.8 (18.1)	94.5 (22.0)	96.7 (19.4)***	110.2 (14.3)	109.1 (12.1)	109.7 (13.4)***
FSIQ	99.6 (15.4)	97.3 (20.4)	98.8 (17.1)***	109.5 (12.6)	108.6 (10.4)	109.1 (11.7)***

Note. Values are given as Mean (Standard Deviation) unless otherwise denoted. NVIQ=non-verbal IQ; VIQ=verbal IQ; FSIQ=full scale IQ.
*$p < 0.05$. ***$p < 0.001$.

Table 2

Best-fitting multilevel models predicting SST performance

Stopping Accuracy (Logistic Model)

Fixed Effect Estimates		**Random Effect Variances**	
Level 1 variables		Level 2 intercept (μ_{0i})	0.61 (0.78)
Intercept	0.68 (0.08) ***	SSD	0.12 (0.35)
SSD	-0.81 (0.05) ***	Direction	0.44 (0.66)
SSD^2	0.09 (0.04) *		
Level 2 Variables			
Group	-0.39 (0.15) *		
Age	0.23 (0.08) *		

GO RT Slowing

Fixed Effect Estimates		**Random Effect Variances**	
Level 1 variables		Level 1 residual (ε_{it})	5161.3 (71.84)
Intercept	275.09 (2.62)***	Level 2 intercept (μ_{0i})	772.3 (27.79)
Task (Baseline vs. GO trials)	88.93 (3.97)***	Direction	267.9 (16.37)
Level 2 Variables		Task	1657.7 (40.72)
Group	-15.77 (5.25)**		
Age	4.24 (2.67)		
Interaction Variables			
Task x Group	-22.97 (7.96) **		
Task x Age	25.75 (4.05)***		

SSRT

Fixed Effect Estimates		**Random Effect Variances**	
Level 1 variables		Level 1 residual (ε_{it})	915.8 (30.26)
Intercept	150.92 (3.12)***	Level 2 intercept (μ_{0i})	729.2 (27.00)
Level 2 Variables			
Group	-13.32 (6.25)*		
Age	7.85 (3.13)*		

Note. Values are given as Estimate (Standard Error) or Variance (Standard Deviation).
*p < 0.05. **p < 0.01. ***p < 0.001.

Table 3

Stop signal task performance for ASD and TD participants

	ASD (n = 60)	**Controls (n = 63)**
STOP Accuracy (%)	62 (17)	69 (15)
Baseline RT (ms)	230 (34)	235 (35)
GO RT (ms)	304 (43)	333 (45)
Slowing (Baseline – GO RT)	75 (51)	98 (53)
SSRT (ms)[a]	143 (34)	158 (36)

Note. Values are given as mean (standard deviation).
[a]One ASD participant with 0% accuracy in one direction was not included in SSRT analyses.

Table 4

Partial correlations for SST performance and ASD symptoms controlling for age

	Individual Stopping Accuracy Slope		**GO RT Slowing**		**SSRT**	
	$r_{partial}$	Uncorrected p-value	$r_{parital}$	Uncorrected p-value	$r_{partial}$	Uncorrected p-value
ADOS Social-Communication	-0.15	0.36	0.35	0.03	-0.05	0.78
ADI-R Reciprocal Social Interaction	-0.19	0.25	0.09	0.60	0.19	0.26
ADI-R Communication	-0.07	0.66	-0.14	0.38	-0.03	0.84
ADI-R Higher-Level RRB	0.08	0.61	0.02	0.93	0.08	0.64
ADI-R Lower-Level RRB	-0.03	0.84	0.07	0.69	-0.03	0.87
RBS-R Stereotyped	0.24	0.14	0.01	0.96	0.11	0.52
RBS-R Self-injurious	0.23	0.15	-0.06	0.73	-0.05	0.74
RBS-R Compulsive	0.20	0.21	0.04	0.81	0.08	0.63
RBS-R Ritualistic	0.11	0.50	-0.07	0.69	-0.16	0.34
RBS-R Sameness	0.19	0.24	0.09	0.56	0.09	0.59
RBS-R Restricted Behavior	0.19	0.24	<0.01	0.98	<0.01	0.99

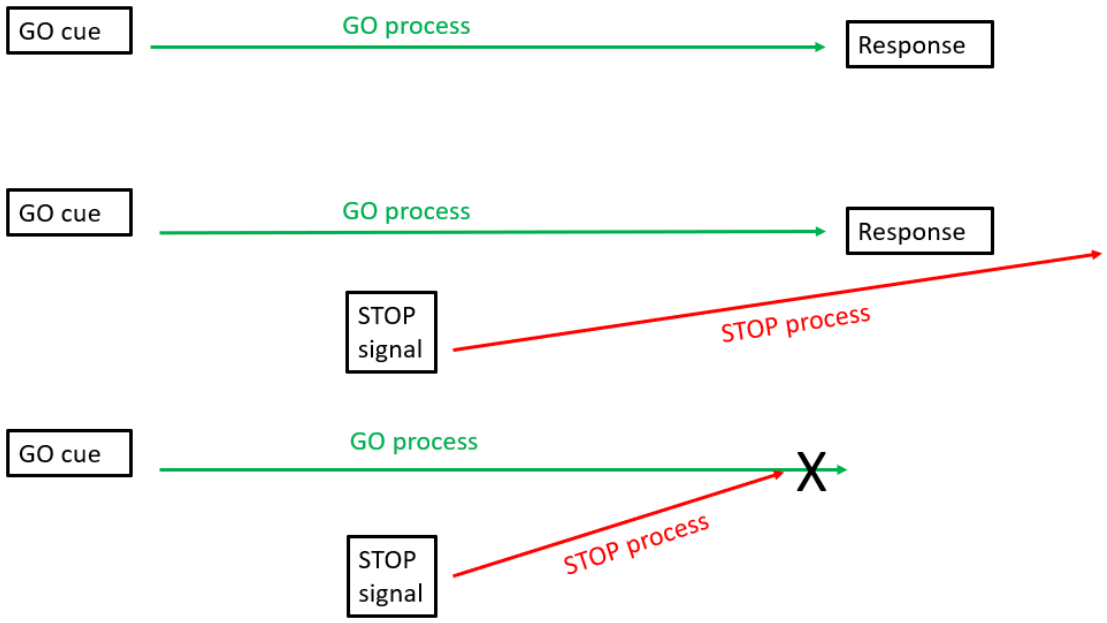

Figure 1. Schematic representation of the independent race model. On GO trials, the GO process is initiated by the appearance of the GO cue and results in a behavioral response. On STOP trials, the STOP process is initiated by the appearance of the STOP signal. If the GO process finishes first, the participant incorrectly responds. If the STOP process finishes first, it inhibits the GO process and the participant does not respond.

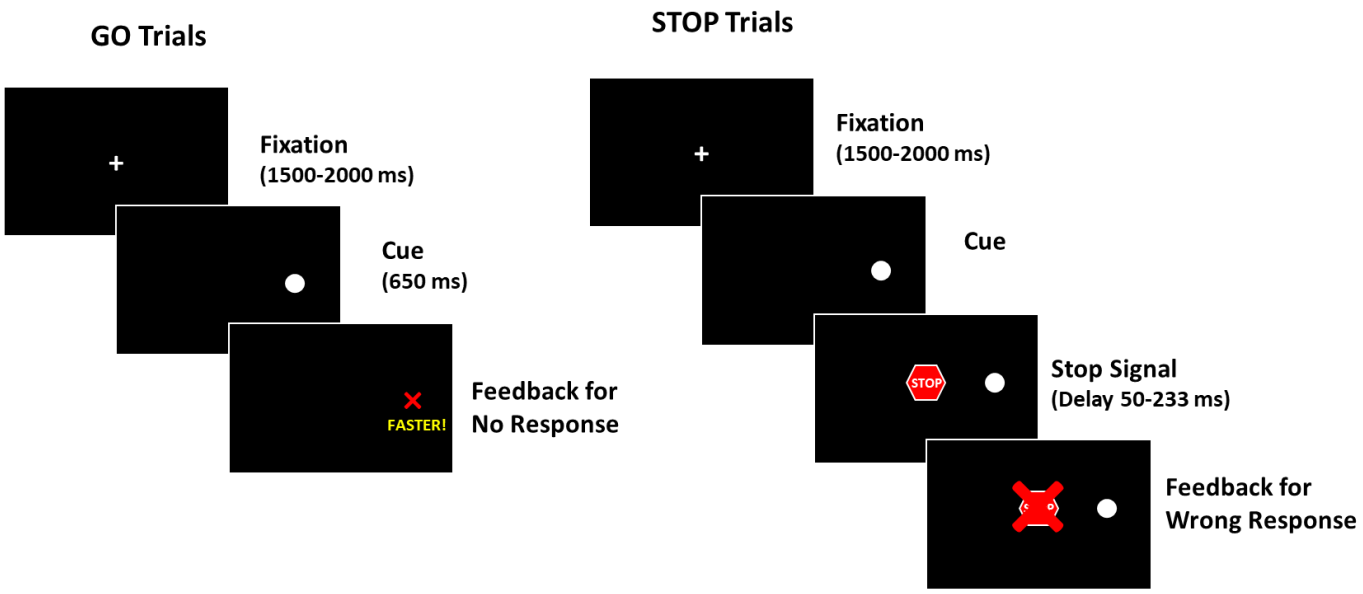

Figure 2. Schematic representation of the SST. Participants fixed on a central crosshair at the start of each trial. On GO trials, participants looked at a peripheral GO cue. If participants did not respond within 650 ms, a red "X" and the word "Faster!" appeared. On STOP trials, the GO cue was followed by a stop signal after a variable interval, instructing participants to inhibit looking toward the GO cue. If participants looked toward the GO cue on a STOP trial, a red "X" appeared.

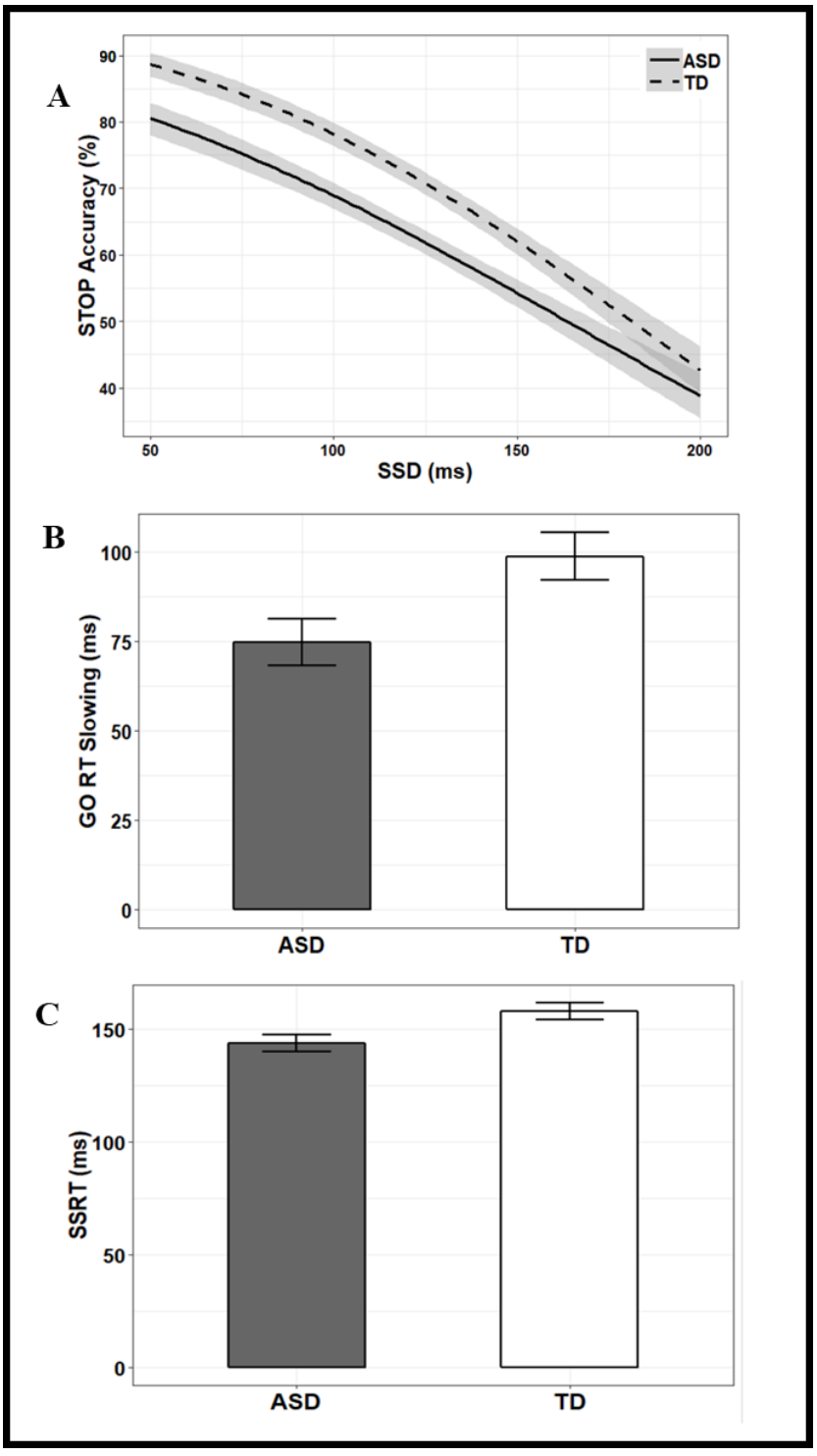

Figure 3. SST performance in ASD and TD participants. Individuals with ASD exhibited reduced stopping accuracy (A), reduced RT slowing on GO trials compared to baseline (B), and shorter SSRTs (C) compared to TD controls.

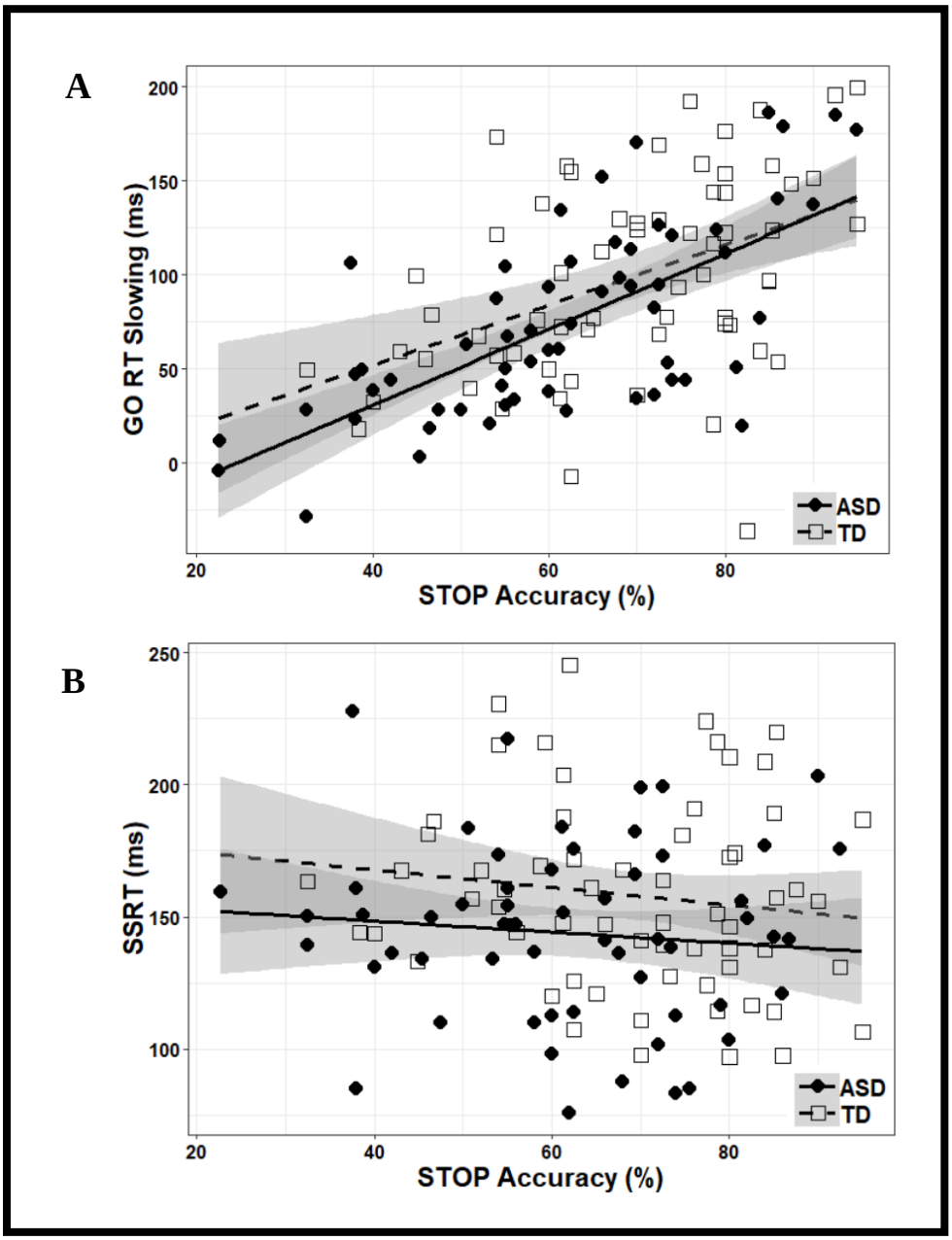

Figure 4. Relationships amongst SST performance variables in ASD and TD participants. Increased RT slowing was associated with higher stopping accuracy in both groups (A). SSRT was not related to stopping accuracy for either group (B).